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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/787,497	BALS ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 21-39* is/are pending in the application.

4a) Of the above claim(s) *36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 21-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants present a new traversal of the restriction requirement. Contrary to applicants assertion, the Examiner did not assert that there was no traversal in the Office Action mailed 8/17/2007. Rather, the Examiner stated: "Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a))." In the traversal filed 6/20/2007, applicants merely asserted that the search would not constitute and undue burden, providing no rationale or evidence for the assertion. No errors in the requirement were pointed out. Contrary to applicants assertion that the only search required was one of sequence, the claims are directed to methods, not sequences.

In response to applicants *current* traversal, the Examiner finds that the specification teaches at paragraph [0019] that LL-37 is a FRPL-1 agonist. Accordingly, claims 29-35 are rejoined to the extent that they read on a FRPL-1 agonist, that being a genus to which the species LL-37 belongs. Claims 36-39 remain withdrawn from prosecution as being drawn to a non-elected invention.

The restriction requirement is made FINAL.

Applicants persuasive argument not having been presented in a timely manner, all new rejections necessitated by the rejoinder of claims 29-35 are considered to be necessitated by applicants amendment filed 11/16/2007.

Claims 2 and 21-35 are under consideration. Claim 29 is objected to for reading on a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 25-27 remain, and claims 29 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record in the previous Office action. It is noted that claim 29 is truly a single means claim, as the agonist is not defined in any way other than activity. Clearly if the narrower claims lack adequate written description, so does the broader.

Applicants traversal of this rejection has been fully considered but is not deemed persuasive for reasons that follow:

At page 4-5 of the response filed 11/16/2007, applicant argues that the term "mutant" has been described at paragraph [0041] of the specification and would be understood by the person of ordinary skill in the art. This argument has been fully considered but is not deemed persuasive because applicants are arguing enablement of mutants, rather than written description of such, which is the basis of this rejection. The specification provides only a vague discussion of mutants. There is no conception of any particular mutant within the scope of the claims. All that exists is an invitation to discover such mutants. While such discovery would not constitute undue experimentation (and hence no rejection was made under 35 U.S.C. §112, first paragraph on the basis of lack of enablement), there is no conception of the mutants so discovered until the work is actually done. This fact situation is similar to that in *Amgen v. Chugai* (18 USPQ 2d 1017, 1991), in which it was found that conception may not be achieved until reduction to practice in cases involving cloning genes. In this case a gene is not being cloned. Rather, a single peptide is disclosed, and an invitation to imagine functional muteins thereof is issued. Particular muteins thereof cannot be envisioned, and therefore are not conceived, until they are reduced to practice. The fact that there may be trivial modifications within the metes and bounds of the claims does not overcome the fact that there is no upper limit on the number or types of modifications, such that the claim amounts to a single means claim. The description of a single species is not sufficient to support the claim.

At page 5, applicants argue the meaning of the term "derivative" stating that such is clearly defined at paragraph [0049]. It is noted that this paragraph is much broader than the paragraph pertaining to mutants, and as such, is not persuasive for reasons cited above.

Also at page 5, applicants argue that peptidomimetics are clearly described at paragraph [0047]. While it is true, as argued by applicants that a peptidomimetic includes a peptide with a different backbone or comprising D amino acids, paragraph [0047] does not disclose these types of modifications. The paragraph in question describes the finding of peptides that have the sole specified property of being angiogenesis stimulating, such as would be discovered by computational methods, or by screening a combinatorial library. Clearly there is no description of any peptide that might be found via such screening. Accordingly, this argument, too, is not persuasive.

Applicants arguments at page 6 are solely directed to issues of enablement, and are not pertinent to the rejection at hand, which is one of written description. Applicants argument that the claims would be too easily infringed, or that peptidomimetics would not be allowable in future cases in view of the KSR standards of obviousness have been fully considered but are not deemed persuasive. These positions are conjectural, and not pertinent to the issue at hand. Argument cannot take the place of an adequate written description as required by 35 U.S.C. §112, first paragraph. Further, obviousness of as yet undiscovered compounds cannot be determined, nor is it pertinent. With regard to applicants arguments that others have made D amino acid derivatives of LL-37, the Examiner cannot find the term D amino acid in the instant specification. With regard to applicants arguments pertaining to angiogenic fragments of SEQ ID NO: 1, the Examiner notes that such fragments were specifically excluded from this rejection.

The specification as filed does provides written description only of SEQ ID NO: 1. It additionally reasonably conveys written description of fragments of SEQ ID NO: 1 that retain angiogenic activity. However, the claims broadly read on any LL-37 receptor agonist, including "derivatives", "peptidomimetics" and "mutants" of such. The specification neither defines such terms in a manner that one could determine the metes and bounds of the invention, nor is there any written description of any derivative, peptidomimetics nor mutant of SEQ ID NO: 1. Accordingly, the written description is not commensurate in scope with the claims.

Finally, citing MPEP 2144.03, applicants request that the Examiner file a declaration of affidavit articulating the rationale that "the making of a mutant, derivative or peptidomimetic was not conceived by inventors and that the inventors description of same is insufficient to communicate to one skilled in the art what the invention is." This argument has been fully considered but is not deemed persuasive. MPEP 2144.03 pertains to "reliance on common knowldedge in the art or "well known" prior art", which is not an issue in this rejection. The Examiner has taken no official notice of prior art teachings, and this is not a prior art rejection.

It remains that with the exception of the SEQ ID NO: 1 or fragments thereof, the skilled artisan cannot envision the detailed chemical structure of the encompassed LL-37 receptor agonists used in the claimed method, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only proteins comprising SEQ ID NO: 1 or a fragment thereof with angiogenic activity, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Arguments pertaining to enablement or prior art are simply not persuasive.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22 and 25-27 remain, and claims 29 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As stated above, the specification does not provide an adequate written description of the active molecules to be used in the claimed methods. Since the active agents are not described, the person of ordinary skill in the art cannot determine the metes and bounds of the claims. Merely claiming administration of an agent having a given activity is not sufficient to set forth the metes and bounds of those agents within the scope of the claims. With particular respect to claim 29, such is a single means claim that provides no structure or other characteristics other than a biological activity to define the active agent, such that the metes and bounds of the claim cannot be determined.

This rejection is maintained for reasons of record. Applicants argue that "no particular term or phrase is pointed to as having a meaning that is unclear." This argument has been fully considered but is not deemed persuasive. The rejection, as reproduced in full above, is on the basis that the metes and bounds of that which is not described cannot be determined. The statute does not require identification of particular terms in the claims, merely a clear indication of why the metes and bounds of the claims cannot be determined. It is not possible to search for undescribed compounds, and the metes and bounds of the claims cannot be determined without knowing what compounds are used. Mere recitation of a function (angiogenesis stimulating) is not sufficient to convey the metes and bounds of the claims.

Rejections over Prior Art

Prior to setting forth the prior art rejections, the following observations are made on interpretation of the claims:

LL-37 is well-known in the art, and SEQ ID NO: 1 of the instant application consists of the art-recognized sequence for such. Accordingly, art that refers to LL-37 but does not list the sequence is presumed to intend SEQ ID NO: 1.

In applying the prior art, the Examiner has interpreted any variant of LL-37 to be a "derivative", "peptidomimetic" or "mutant".

It is presumed that administration of a pharmaceutically acceptable amount of LL-37 will inherently increase angiogenesis, that property being an inseparable feature of the peptide itself.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 and 21-35 are rejected under 35 U.S.C. 103(a) as being obvious over Larrick et al., U.S. Patent No. 5,618,675 in view of Lehrer et al., Curr. Opin. Hematol. 9:18-22, previously of record, and Whitman et al., U.S. Patent No. 5,470,831, and further in view of Wu et al,. Inf. and Imm. 68:5552, 2000.

Larric et al. teach LL-37, which they designate the "RNIP fragment of the CAP18 molecule". At column 6 lines 43+, Larric et al. teach the use of polypeptides "which comprise at least the active portion of the RNIP fragment of the CAP18 molecule and those which comprise substantially the entire CAP18 molecule." At column 7, they define the RNIP fragment as amino acids 137-170 of SEQ ID NO: 2, which is identical in sequence and length to SEQ ID NO: 1 of the instant application. They further teach substitution of amino acids in RNIP with, for example corresponding amino acids from the rabbit homologue (col. 7, lines 13-17). At the paragraph bridging columns 9-10, Larric et al. teach that the polypeptides may be used "to attenuate, inhibit or prevent LPS-associated conditions, such as Gram-negative sepsis, autoimmune disorders, inflammation and the like." Larric et al. do not teach the use of LL-37 for administration to a patient in need of increased angiogenesis.

Lehrer et al., Curr. Opin. Hematol. 9:18-22, previously of record, teaches that LL-37 is chemotactic for human neutrophils, monocytes and lymphocytes, and that hCAP-18 is induced after injury, such as incision.

Whitman teaches, in the abstract of the patent, that "The angiogenic peptides of the invention may be particularly useful in promoting wound healing, including incisional healing, bone repair, burn healing, and post-infarction repair in myocardial injury, and in facilitating the assimilation of grafted tissues, particularly in persons suffering from vascular insufficiency, such as diabetic patients."

Wu et al. teach that cathelicidins (of which LL-37 is the only known human form) "have been implicated in wound healing, angiogenesis, and other innate immune mechanisms".

Accordingly, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the peptide of Larric et al. to treat wound healing or incision, as suggested by Lehrer et al. Whitman provides evidence that a person with a wound or incision is in need of angiogenesis. Wu provides a further expectation of success in view of

the disclosure that cathelicidins have been implicated in wound healing and angiogenesis. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Claims 22 and 25-29 and 32-35 are rejected under 35 U.S.C. 103(a) as being obvious over Hirata, U.S. Patent No. 6,040,291 in view of Lehrer et al., Curr. Opin. Hematol. 9:18-22, previously of record, and Whitman et al., U.S. Patent No. 5,470,831 , and further in view of Wu et al,. Inf. and Imm. 68:5552, 2000.

Hirada teaches numerous fragments of SEQ ID NO: 1 of the instant specification, which fragments are stated to have antimicrobial activity: see column 16, Table 1 for example. The claims are drawn to bacterial-infection treating compositions comprising such peptides (claims 7, 8) and methods of treatment of bacterial infection or endotoxin shock using such peptides (claims 13, 14). In view of the above claim interpretation comments, the fragments of Hirada meet the limitations of the claims. Hirada et al. do not teach the use of LL-37 for administration to a patient in need of increased angiogenesis.

The teachings of Lehrer et al., Whitman and Wu are summarized above. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the peptides of Hirada et al. to treat wound healing or incision, as suggested by Lehrer et al. Whitman provides evidence that a person with a wound or incision is in need of angiogenesis. Wu provides a further expectation of success in view of the disclosure that cathelicidins have been implicated in wound healing and angiogenesis. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

It is noted that Hirada is silent with respect to angiogenic properties of the disclosed fragments. Applicants claim the use of fragments of LL-37 (without any showing of which fragments have angiogenic activity), and several of Hirata's fragments comprise the majority of the LL-37 peptide. Since the Office does not have the facilities for examining and comparing the peptides of the prior art to determine which of them retain angiogenic properties, the burden is on applicant to show a novel or unobvious difference between the product used in the claims and the products of the prior art (i.e., that the peptides of the prior art does not possess the same material structural and functional characteristics of the peptides used in the claimed methods).

See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claims 2, 21-24 and 28-31 are rejected under 35 U.S.C. 102(e) as being obvious over Chertov et al., U.S. Patent Application Publication No. 2002/0072495 in view of Lehrer et al., Curr. Opin. Hematol. 9:18-22, previously of record, and Whitman et al., U.S. Patent No. 5,470,831, and further in view of Wu et al,. Inf. and Imm. 68:5552, 2000.

Chertov et al. teach the use of LL-37 for boosting the immune response to conditions such as bacterial infection and viral infection; see paragraph [0027]. At paragraph [0029], dosages consistent with those in the instant specification are discussed. Claims 1-6 are drawn to a method of enhancing an immune response in subject, comprising administration of LL-37. Chertov et al. do not teach the use of LL-37 for administration to a patient in need of increased angiogenesis.

The teachings of Lehrer et al., Whitman and Wu are summarized above. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the peptides of Chertov et al. to treat wound healing or incision, as suggested by Lehrer et al. Whitman provides evidence that a person with a wound or incision is in need of angiogenesis. Wu provides a further expectation of success in view of the disclosure that cathelicidins have been implicated in wound healing and angiogenesis. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/
Primary Examiner, Art Unit 1647